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A FLUOROISOPRENYLATION SEQUENCE EMPLOYING 2-FLUOROALKENAL DERIVED AZOMETHINES AS KEY INTERMEDIATES : A STEREOCONTROLLED SYNTHESIS OF 2-FLUOROGERANIOL AND 2-FLUOROFARNESOL

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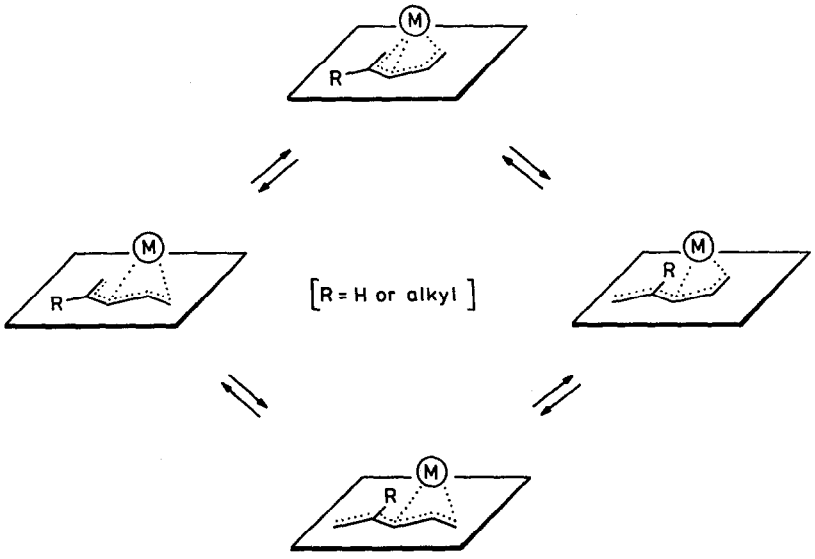
Summary : Azomethines (Schiff's bases) derived from α,β-unsaturated α-fluoroaldehydes can be deprotonated with lithium diisopropylamide. The resulting "anions" or, correctly, 3-fluoro-1-azapentadienyl lithium compounds are conformationally mobile. While eight different coplanar structures are possible, one of them, a zigzag shaped *(W)* conformation must be largely favored. - Depending on their nature, electrophiles attack the 1-azapentadienyl intermediates at either of the three nodal points : the nitrogen atom, the fluorine bearing α-position or the terminal γ-position. Allyl type alkylating reagents produce a mixture of α- and γ-regioisomers from which the pure components can be separated. Consecutive hydrolysis and reduction provides α-fluoroalkenals and α-fluoroallyl alcohols.

Pentadienyl type organometallics can exist in three or four resonance stabilized and hence privileged structures. The required coplanarity can be achieved by horseshoe like *(U)*, sickle like *(S)* and zigzag-like *(W)* conformations. If the two wings of the pentadienyl moiety are asymmetrically substituted (*e.g.*, by an alkyl group R at the 2-position) the degeneracy of the sickle-shape is removed and two non-identical *S* and *S'* conformations have to be considered, one carrying the substituent at the blade, the other at the handle of the sickle. [1, 2]

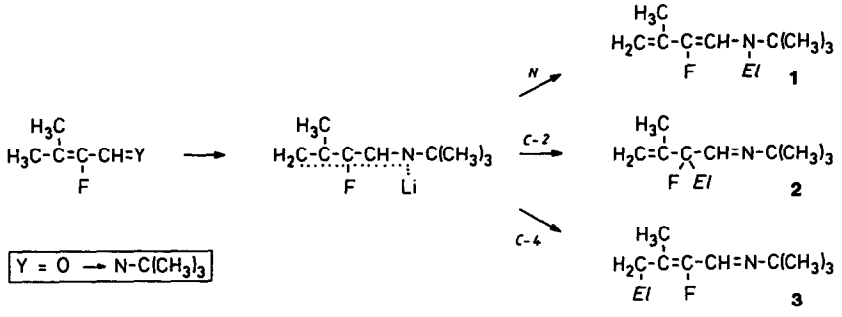


The rotation around an internal (C-2/C-3 or C-3/C-4) carbon-carbon bond of the pentadienyl moiety occurs quite readily at temperatures above -60 °C [1]. Therefore, a rapid dynamic equilibrium between the privileged conformations is established under ordinary conditions. As chemical and spectroscopic investigations have revealed, most pentadienylmetal derivatives are accomodated in the *W* conformation preferentially if not exclusively. Notable exceptions are pentadienyl, *exo*-1-alkylpentadienyl and 2-alkylpentadienyl *potassium* compounds as well as 2,4-dialkylpentadienyl *potassium* or *lithium* which all favor the *U* shape. [1-3]

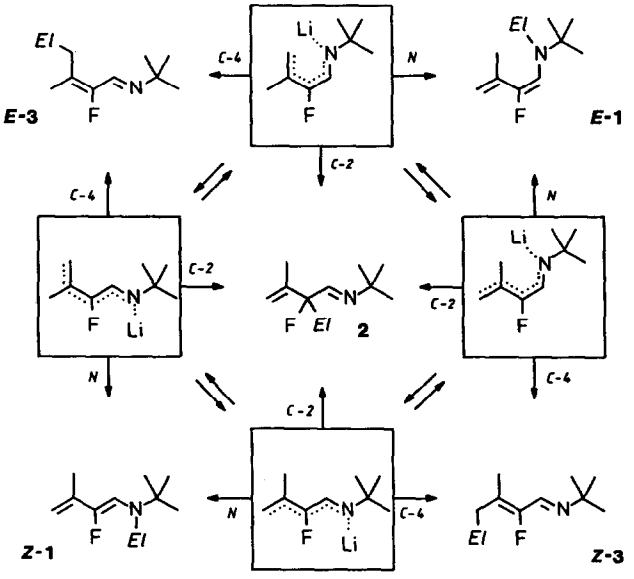
When devising the fluoroisoprenylation sequence [4], we expected the key intermediate, 1-aza-3-fluoro-4-methylpentadienyl lithium, again to adopt the *W* shape as required. This assumption is plausible. While the fluorine substituent should exert only a small effect, the nitrogen atom must cause a major perturbation of the electron distribution in the pentadienyl moiety. Negative charge being accumulated at the heteroelement, a metal such as lithium or even potassium will abandon its π-type (η^3 or η^5) [5] interaction with the organic backbone and rather install a σ-bond. Under these circumstances, *U* and *S* structures present only disadvantages and should no longer be able to compete with *W* conformations. Actually an nmr study showed potassium 2,4-pentadienolate ("1-oxapentadienyl potassium") to occupy the "*W*" shape if in liquid ammonia. [6]. In view of this highly dissociative medium, however, the comparison with our lithium dienamides ("1-azapentadienyl lithium" species) in ethereal solution may be considered as too farfetched. Moreover, a spectroscopic approach will generally allow to detect the major conformer but not identify minor components beyond doubt. Therefore, we decided to probe the structure of 1-azapentadienyl species by correlating their various conformations with the configurations of derivatives formed upon their interception with electrophiles.

The Conformational Preference of Lithium 2-Fluoro-1,3-dienamides

The approach will be illustrated taking the aldimine resulting from the condensation of 2-fluoro-3-methyl-2-butenal [7] with *tert*-butylamine as a model case. Its deprotonation with lithium diisopropylamide in tetrahydrofuran generated lithium *N-tert*-butyl-(2-fluoro-3-methyl-1,3-butadienyl)amide as a colorless, perfectly soluble intermediate. The latter species was then trapped by a variety of electrophiles which attacked at one of the three electron-rich centers, either at the nitrogen or at the carbon-2 or the carbon-4 atom. Depending on the nature of the electrophile chosen, a single regioisomer (**1**, **2** or **3**) or a mixture consisting of two or three components was formed.

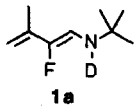


Whereever the electrophile becomes attached, it will suppress the bond averaging charge delocalization, fixing simple and double bonds in alternation. The configuration of the double bonds now provides all the information to elucidate the conformation of the lithiated procursors. For example, if the electrophile attacks the nitrogen and produces a new double bond between C-1 and C-2 which has the *(E)* configuration, this could be traced back to either a *U*- or an *S'*-shaped intermediate. If then another electrophile gets linked to the terminal carbon atom and gives rise to a permanent double bond betrween D-3 and C-4 having a *(Z)* configuration, this would be compatible with either an *(S')* or a *(W)* conformation. The latter, however, has to be ruled out in order to satisfy also the previous findings. Only the regioisomers **2**, which carry the electrophile in the middle of the former azapentadienyl moiety, have lost all their stereochemical history. They could only serve to certify the *(E)* configuration of the azomethine function, though this is not really an open question. Due to the steric bulk of the *tert*-butyl group [8], it may be safely assumed always to occupy the *trans* (or *exo*) position. Otherwise we would have to deal with eight rather than four privileged conformations.

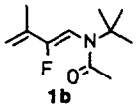


When the lithiated *N*-(2-fluoro-3-methyl-2-butenylidene)-*tert*-butyl-amine was allowed to react with deuterium oxide, acyl chloride and chlorodiphenylphosphine, pure regioisomers **1a** and **1b** were formed. Previously Oppolzer *et al.* [9] had shown lithium *N*-(*tert*-butyl)-1,3-butadienylamide, *i.e.* deprotonated *N*-(2-butenylidene)-*tert*-butylamine, to undergo exclusive acylation at the heteroatom. Simultaneously Japanese workers [10] had reported the same species as well as its 3-methyl branched homologue to afford selectively the *N*-silylated derivatives when treated with chlorotrimethylsilane. With our intermediate, however, a 1 : 2 mixture of the C-4- and *N*-silylated compounds **1c** and **3c** was isolated. A 4 : 1 mixture of alkylation products **2d** and **3d** resulted from the reaction with dimethyl sulfate, while methyl iodide gave exclusively **2d**. Schlessinger *et al.* [11] had

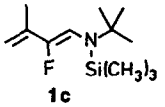
formerly studied the alkylation of lithiated *N*-(2-butenylidene)-cyclohexylamine using half a dozen of different organic halides and never observed electrophilic attack at another position than at C-2. Finally chlorodiphenylphosphine proved highly regioselective in favor of the terminal C-4 position, leading to the phosphine **3e**.



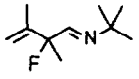
1a



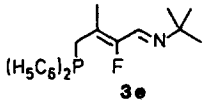
1b



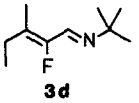
1c



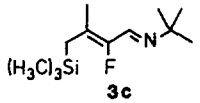
2d



3e



3d



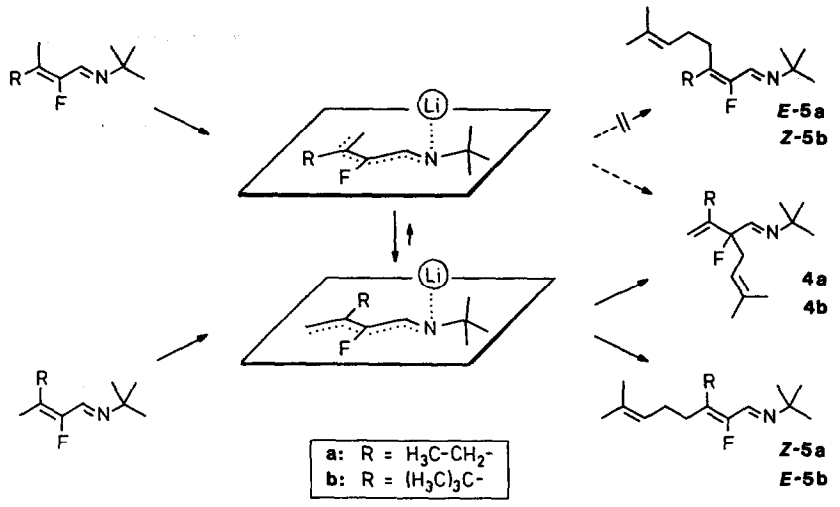
3c

As evidenced by ^{1}H- and ^{19}F-nmr spectroscopy, all derivatives **1** and **3** were pure stereoisomers having the *(Z)* configuration in both series. This allows us to conclude that only the *W* conformer of the lithiated *tert*-butyl-*N*-(2-fluoro-3-methyl-2-butylidene)amine is populated to a significant extent.

The Conformational Mobility of Lithium 2-Fluoro-1,3-dienamides

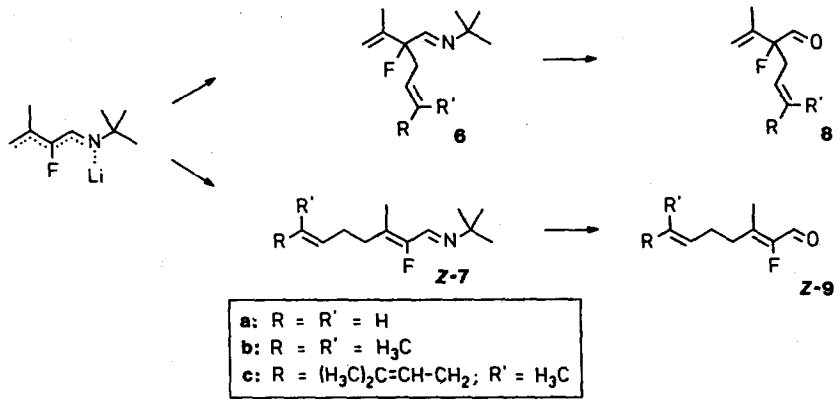
One might, of course, have argued in a different way. Could the preponderance of the *W* conformer not simply reflect a higher kinetic acidity of the allylic methyl group occupying the *cis* position with respect of the halogen atom in conjunction with a frozen conformational equilibrium ? In order to refute this objection we had to demonstrate the conformational mobility of the lithiated azomethanes. This was achieved by using stereoisomers that would have to generate an *S*- (or *U*-) shaped intermediate upon deprotonation.

To this purpose, we have prepared a 3 : 2 *(Z/E)* mixture of *tert*-butyl-*N*-(2-fluoro-3-methyl-2-pentenylidene)-amine. This could be accomplished by an acid catalyzed isomerization of the methylation product **3d** isolated as a pure (*Z*) isomer (see above). Alternatively, the same (*Z/E*) mixture could be produced by solvolytic ring opening [7] of 1-chloro-1-fluoro-2-ethyl-3-methoxy-2-methylcyclopropane followed by condensation of the resulting aldehyde (*Z/E* = 3 : 2) with *tert*-butylamine. After selective [12] deprotonation of the allylic methyl group in both geometrical azaomethine isomers with lithium diisopropylamide and subsequent alkylation with 3-methyl-2-butenyl ("prenyl") bromide, a 60 : 40 mixture of the C-2 branched and the C-4 chain lengthened regioisomer (**4a** and **5a**, respectively) was obtained, the hydrocarbon chain of the latter having exclusively the *trans* configuration (*Z*-**5a**). Even more conclusive was a similar study with *tert*-butyl-*N*-(2-fluoro-3,4,4-trimethyl-2-pentenylidene)-amine as the starting material, since this compound was accesible as a pure *(Z)* isomer. After consecutive treatment with lithium diisopropylamide and with prenyl bromide the (*Z*) and the *(E)* isomer (*E*-**5b**) of the chain lengthened product **5b** was formed as the principal product, besides the branched regioisomer **4b**. Thus, the conformational mobility of "1-azapentadienyl lithium" intermediates has been compellingly demonstrated.

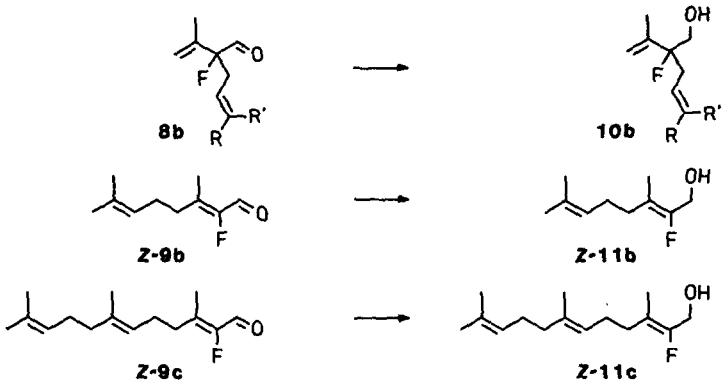


Fluoroterpenoids by Allylation of Lithium 2-Fluoro-1,3-dienamides

The concomitant attack of prenyl bromide at the C-2 and C-4 position, producing a mixture of regioisomers **4** and **5** was not to be expected since halogen free lithium *N-tert*-butyl-(3-alkyl-1,3-butadiene)amides were reported to react with prenyl chioride to give virtually pure branched derivatives [10]. Therefore we wanted also to study the behavior of lithium *N-tert*-butyl-(2-fluoro-3-methyl-1,3-butadiene)amides itself towards allyl type alkylating agents. When treated with allyl, prenyl and geranylbromide, it invariably afforded mixtures of branched and chain elongated products (**6** and **7**, respectively) in ratios varying from 3 : 2 to 1 : 1. The latter regioisomers were again stereochemically homogeneous, having the *(Z)* configuration. Acid hydrolysis converted the azomethines **6** and *Z*-**7** into the regioisomeric aldehydes **8** and *(Z)*-**9** which could be readily separated by chromatographic means.



Finally, the aldehydes have been reduced to the corresponding allyl alcohols. The branched regioisomer **8b** gave 2-fluorolavandulol (**10b**); the chain-elongated derivatives *(Z)*-**9b** and *(Z)*-**9b** afforded 2-fluorogeraniol *(Z)*-**11b** and 2-fluorofarnesol *(Z)*-**11c**.



These examples illustrate the principle features of the fluoroisoprenylation sequence disclosed in the present work. Its major appeal is the perfect stereocontrol which can be exerted. On the other hand, its lack of regioselectivity constitutes a certain drawback although the latter is attenuated by the ease with which the branched and chain elongated products can be chromatographically separated.

EXPERIMENTAL PART

1. Generalities

For standard laboratory practice, techniques and abbreviations, see related articles, *e.g.* ref. [13].

2. Starting Materials

a) 2-Fluoro-2-alkenals

Working procedure [14] : At -15 °C, a flask carrying a dry ice condenser was filled with 1,4,7,10,13,16-hexaoxacyclooctacane ("18-crown-6"; 0.80 g, 3.0 mmol), a 55% aqueous solution (50 mL, 1.2 M) of potassium hydroxide (73 mmol), the enether (0.10 mol) and dichlorofluoromethane (21 mL, 30 g, 0.30 mol). After 3 h of vigorous magnetic stirring at 0 °C, the organic layer was decanted and the aqueous phase extracted with diethyl ether (2 × 50 mL). After evaporation of the solvent, water (50 mL) containing some sodium dodecylsulfate (sodium "laurylsulfate", 0.5 g) and hydroquinone (0.1 g) was added. The suspension was heated 7 h to reflux. Extraction with diethyl ether (3 × 20 mL), drying filtration and distillation afforded the desired product.

2-Fluoro-3-methyl-2-pentenal : 57% (from 1-methoxy-2-methyl-1-butene [15]); bp 58 - 60 °C/60 mmHg; *(Z/E)* ratio of 60 : 40 according to gas chromatography (40 m C-20 M, 80 °C; 20 m SE-30, 60 °C) and nmr. - ^{1}H-NMR (80 MHz) : δ 9.60 (1 H, d, J 16), 2.4 (2 H, m), 2.05 (0.6 × 3 H, d, J 3), 1.90 (0.4 × 3 H, d, J 4), 1.10 (0.6 × 3 H, t, J 7), 1.05 (0.4 × 3 H, t, J 7). - ^{19}F-NMR (84, 7 MHz) : -57 (0.4 × 1 F, d, J 17), -58 (0.6 × 1 F, d, J 18). - MS (180 °C) : 116 (6%, M^+), 59 (100%). - Analysis : calc. for C_6H_9FO (116.13) C 62.05, H 7.81; found C 61.96, H 7.91%.

2-Fluoro-3,4,4-trimethyl-2-pentenal : 70% (from 1-methoxy-2,3,3-trimethyl-1-butene [16]); bp 82 - 85 °C/25 mmHg. - ^{1}H-NMR (360 MHz) : δ 9.81 (1 H, d, J 15.8), 2.11 (3 H, d, J 3.3), 1.25 (9 H, d, J 2.9). - Analysis : calc. for $C_8H_{13}FO$ (144.19) C 66.64, H 9.09; found C 66.31, H 9.18%.

b) Azomethines

Working procedure : The 2-fluoro-2-alkenal (0.10 mmol) was added to *tert*-butylamine (1,2-dimethylethylamine, 12 mL 8.3 g, 0.11 mol) at 0 °C. The mixture was allowed to stand 2 h at 25 °C in the presence of powdered potassium hydroxide (1.0 g, 18 mmol) before being distilled under reduced pressure.

tert-Butyl-*N*-(2-fluoro-3-methyl-2-butenylidene)amine : 70%; bp 85 - 90 °C/35 mmHg. - ^{1}H-NMR (80 MHz) : δ 8.10 (1 H, d, *J* 18), 1.90 (3 H, d, *J* 3), 1.87 (3 H, d, *J* 4), 1.25 (9 H, s). - ^{19}F-NMR (84.7 MHz) : -48 (d, hept, *J* 18, 3). - MS (150 °C) : 159 (9%, M^+), 101 (100%). - Analysis : calc. for $C_9H_{16}FN$ /157,27) C 68.75, H 10.26; found C 68.86, H 10.24%.

tert-Butyl-*N*-(2-fluoro-3-methyl-2-pentenylidene)amine : 71%; bp 69 - 70 °C/12 mmHg, *(Z/E)* ratio of 60 : 40 according to gas chromatography (2 m, 3% SE-30, 120 °C; 2 m, 20% C-20 M, 120 °C) and nmr. - ^{1}H-NMR (80 MHz): δ 7.95 (1 H, d, *J* 19), 2.2 (2 H, m), 1.90 (0.6 × 3 H, d, *J* 3), 1.85 (0.4 × 3 H, d, *J* 4), 1.25 (9 H, s), 1.20 (0.6 × 3 H, t, *J* 7), 1.10 (0.4 × 3 H, d, *J* 7). ^{19}F-NMR (84.7 MHz) : -50 (0.4 × 1 F, d, *J* 21), -52 (0.6 × 1 F, d, *J* 20). - MS (180 °C) : 171 (6%, M^+),100 (100%). - Analysis : calc. for $C_{10}H_{18}FN$ (171.2) C 70.13, H 10.59; found C 70.30, H 10.60%.

tert-Butyl-*N*-(2-fluoro-3,4,4-trimethyl-2-pentenylidene)amine : 57%; bp 62 - 65 °C/1 mmHg. - ^{1}H-NMR : (360 MHz) : δ 8.06 (1 H, d, *J* 18.1), 1.88 (3 H, d, *J* 2.8), 1.28 (9 H, s), 1.23 (9 H, d, *J* 1.7). - Analysis : calc. for $C_{12}H_{22}FN$ C 72.32, H 11.13; found C 72.46, H 11.15%.

3. Azomethine Type Substitution Products

Working procedure : At 0 °C, tetrahydrofuran (40 mL), diisopropylamine (4.3 mL, 3.0 g, 30 mmol) hexamethylphosphoric triamide (5.3 mL, 5.4 g, 30 mmol) and the fluorinated azomethane (30 mmol) were consecutively added to a 1.5 M solution of butyllithium (30 mmol) in hexane (20 mL). The mixture turned immediately cherry-red. After 3 h at 0 °C, it was cooled to -75 °C and the electrophile (30 mmol) added. After dilution with diethyl ether (30 mL), the organic phase was thoroughly, though rapidly washed wit ice-water (5 × 20 mL), dried and evaporated. A first nmr spectrum was taken of the crude product which then was purified by distillation or chromatography.

tert-Butyl-*N*-(2-fluoro-3-methyl-1,3-butadienyl)-*N*-[^{2}H]amine (1a) : Approx. 70% (with deuterium oxide). - ^{1}H-NMR (80 MHz) : δ 5.65 (1 H, d, *J* 27), 4.87 (1 H, s, broad), 4.5 (1 H, m), 1.77 (3 H, s, broad), 1.20 (9 H, s). - ^{19}F-NMR (84.7 MHz) : -71 (d, *J* 27). - MS (180 °C) : 158 (3%, M^+), 101 (100%).

N-tert-Butyl-*N*-(2-fluoro-3-methyl-1,3-butadienyl)acetamine (1b) : 86% (with chlorotrimethylsilane). - ^{1}H-NMR (80 MHz) : δ 5.60 (1 H, d, *J* 25), 4.90 (1 H, s), 4.5 (1 H, m), 2.05 (3 H, s), 1.77 (3 H, s, broad), 1.25 (9 H, s). - ^{19}F-NMR (84.7 MHz) : -52 (d, *J* 23).

tert-Butyl-*N*-(2-fluoro-3-methyl-1,3-butadienyl)-*N*-(trimethylsilyl)amine (1c) : Major component of a 2 : 1 mixture (approx. 80%) obtained with acetyl chloride. - ^{1}H-NMR : δ 5.70 (1 H, d, *J* 27), 4.70 (1 H, s, broad), 4.6 (1 H, m), 1.90 (3 H, s), 1.00 (9 H, s), 0.10 (9 H,s). - ^{19}F-NMR (84.7 MHz) : -71 (d, *J* 27).

tert-Butyl-*N*-(2-fluoro-3-methyl-4-trimethylsilyl-2-butenylidene)amine (3c) : Minor component of a 2 : 1 mixture (approx. 80%) obtained with acetyl chloride. - ^{1}H-NMR (80 MHz) : δ 8.07 (1 H, *J* 20), 2.00 (3 H, d, *J* 3), 1.8 (2 H, m), 1.35 (9 H, s), 0.20 (9 H, s). -^{19}F-NMR (84.7 MHz) : -50 (d, *J* 18).

tert-Butyl-*N*-(2-fluoro-2,3-dimethyl-3-butenylidene)amine (2d) : Major component of a 4 : 1 mixture (71%) obtained with dimethyl sulfate. - ^{1}H-NMR (60 MHz) : δ 7.60 (1 H, d, *J* 9.5), 5.14 (1 H, s, broad), 5.00 (1 H, symm. m), 1.75 (3 H, s), 1.56 (3 H, d, *J* 22), 1.20 (9 H, s). - ^{19}F-NMR (84.7 MHz) : -77 (qd, *J* 21, 9). - MS (150 °C) : 173 (0.2%, M^+), 157 (10%), 57 (100%). - Analysis : calc. for $C_{10}H_{18}FN$ (173.2) C 70.15, H 10.52; found C 70.36, H 10.62%.

(Z)-tert-Butyl-*N*-(2-fluoro-3-methyl-2-pentenylidene)amine (3d) : Minor component of a 4 : 1 mixture (71%) obtained with dimethyl sulfate. - Identification as the *(Z)* isomer by acid hydrolysis (see Section 4) followed by gas chromatographic and nmr spectroscopic comparison with the two stereoisomeric 2-fluoro-3-methyl-2-pentenals described above (Section 2).

tert-Butyl-*N*-(4-diphenylphosphinoyl-2-fluoro-3-methyl-2-butenylidene)amine (3e) : 42% (with chlorodiphenylphosphine, subsequently treated with a large excess of 30% aqueous hydrogen peroxide during 1 h at 25 °C;

eluted with toluene from silica gel; apparently the material underwent a 1 : 1 *(Z/E)* equilibration during the chromatography; mp 228 - 239 °C (dec.). - ^{1}H-NMR : δ 7.8 (5 H, m), 7.4 (6 H, m), 3.62 (0.5 × 2 H, d, J 14), 3.30 (0.5 × 2 H, dd, J 14, 3), 2.10 (0.5 × 3 H, t, J 3), 1.90 (0.5 × 3 H, t, J 4), 1.22 (0.5 × 9 H, s), 1.20 (0.5 × 9 H, s). Upon acid hydrolysis (see Section 4) the corresponding aldehyde was formed as a 1 : 1 mixture of *(Z)* and *(E)* isomers; 82%, mp 115 - 129 °C (from toluene). - Analysis : calc. for $C_{17}H_{16}FO_2P$ (302.28) C 67.55, H 5.33; found C 67.74, H 5.41%. - ***(E)*-4-Diphenylphosphinoyl-2-fluoro-3-methyl-2-butenal** : ^{1}H-NMR (80 MHz) : δ 9.20 (1 H, d, J 7), 7.7 (10 H, m), 3.58 (2 H, dd, J 14, 2), 2.00 (3 H, t, J 4). - ^{19}F-NMR (84.7 MHz) : -42 (s, broad). - ***(Z)*-4-Diphenylphosphinoyl-2-fluoro-3-methyl-3-methyl-2-butenal** : ^{1}H-NMR (80 MHz) : δ 9.62 (1 H, d, J 16), 7.7 (4 H, m), 7.5 (6 H, m), 3.30 (2 H, dd, J 15, 3), 2.27 (3 H, t, J 4). - ^{19}F-NMR (84.7 MHz) : -52 (s, broad).

***tert*-Butyl-*N*-[2-(1-ethylvinyl)-2-fluoro-5-methyl-4-hexylidene]amine (4a)** and ***(Z)-tert*-Butyl-*N*-(3-ethyl-2-fluoro-7-methyl-2,6-octadienylidene)amine (*Z*-5a)** : The mixture resulting from the reaction with prenyl bromide was immediately submitted to acid hydrolysis (see Section 4). The resulting aldehydes were isolated by distillation (bp 55 - 60 °C/0.2 mmHg) and separated by preparative gas chromatography (2 m, 5% OV-17, 130 °C). - **2-(1-Ethylvinyl)-2-fluoro-5-methyl-4-hexenal** : ^{1}H-NMR (80 MHz) : δ 9.35 (1 H, d, J 6), 5.1 (3 H, m), 2.60 (2 H, dd, J 25.7), 2.00 (2 H, q, J 7), 1.70 (3 H, s), 1.60 (3 H, s), 1.05 (3 H, t, J 7). - ^{19}F-NMR (84.7 MHz) : -92 (dt, J 25, 6). - Analysis : calc. for $C_{11}H_{17}FO$ (184.25) C 71.71, H 9.30; found C 71.60, C 9.43%. - ***(Z)*-3-Ethyl-2-fluoro-7-methyl-2,6-octadienal** : ^{1}H-NMR (360 MHz) : 9.60 (1 H, d, J 16), 5.10 (1 H, t, J 7), 2.50 (2 H, qd, J 7,2), 2.4 (2 H, m), 2.24 (2 H, t, J 7), 1.72 (3 H, s), 1.60 (3 H, s), 1.16 (3 H, td, J 7.1). - ^{19}F-NMR (84.7 MHz) : -57 (d, J 16). - Analysis : calc. for $C_{11}H_{18}FO$ (184.25) C 71.71, H 9.30; found 71.77, H 9.36%.

***tert*-Butyl-*N*-[2-(1-*tert*-butenylvinyl)-2-fluoro-5-methyl-4-hexylidene]amine (4b)** and ***(E)-tert*-Butyl-*N*-(3-*tert*-butyl-2-fluoro-7-methyl-2,6-octadienylidene)amine (*E*-5b)** in the ratio of 5 : 1 : Again simply a spectrum was recorded of the crude mixture which was then immediately hydrolyzed to afford the corresponding aldehydes. - **4b** : 7.47 (1 H, d, J 11.2), 5.19 (1 H, t, J 7.1), 5.08 (1 H, d, J 4.8), 4.88 (1 H, d, J 1.7), 2.73 (1 H, d, J 7.3), 2.67 (1 H, d, J ~ 7), 1.69 (3 H, s), 1.62 (3 H, s), 1.15 (9 H, s), 1.13 (9 H, d, J ~ 1). - **(*E*-5b)** : 8.34 (1 H, d, J 20.8), 5.19 (1 H, t, J 7.1), 2.2 (2 H, m), 2.1 (2 H, m), 1.28 (9 H, d, J 2.1), 1.25 (9 H, s). - **2-(1-*tert*-Butylvinyl)-2-fluoro-5-methyl-4-hexenal** : δ 9.55 (1 H, d, J 6.9), 5.22 (1 H, d, J 4.5), 5.14 (1 H, thept, J 7.2, 1.5), 4.95 (1 H, d, J 1.7), 2.72 (1 H, dd, J 7.1, 6.4), 2.65 (1 H, d, J 7.1), 1.71 (3 H, d, J ~ 0.5), 1.62 (3 H, s), 1.15 (9 H, d, J 1.4). - ***(E)*-3-*tert*-Butyl-2-fluoro-7-methyl-2,6-octadienal** : δ 10.05 (1 H, d, J 19.2), ~ 5.2 (1 H, t, J ~ 7), 2.3 (2 H, m), 2.2 (2 H, m), 1.36 (3 H, s), 1.28 (3 H, s), 1.13 (9 H, d, J 1.7).

***tert*-Butyl-*N*-[2-fluoro-2-(1-methylvinyl)-4-pentylidene]amine (6a)** : Major component of the 3 : 2 mixture (obtained upon reaction with allyl bromide; 79%; bp 35 - 45 °C/0.2 mmHg) with *Z*-**7a**; separated by preparative gas chromatography (6 m, 5% SE-30, 110 °C). - ^{1}H-NMR (60 MHz) : δ 7.52 (1 H, d, J 10), 5.9 (1 H, m), 5.2 (2 H, m), 5.0 (2 H, m), 2.76 (2 H, dd, J 25, 7), 1.73 (3 H, s, broad), 1.20 (9 H, s). - ^{19}F-NMR (84.7 MHz) : -83 (td, J 24, 11). - MS (150 °C) : 197 (0.3%, M^+), 112 (10%), 57 (100%). - Analysis : calc. for $C_{12}H_{20}FN$ (197.30) C 73.05, H 10.22; found C 73.08, H 10.10%.

***(Z)-tert*-Butyl-*N*-(2-fluoro-3-methyl-2,6-heptadienylidene)amine (*Z*-7a)** : Minor component of the 3 : 2 mixture (obtained upon reaction with allyl bromide; 79%; bp 35 - 45 °C/0.2 mmHg) with **6a**; separated as described above. - ^{1}H-NMR (80 MHz) : δ 8.13 (1 H, d, J 18), 5.8 (1 H, m), 5.2 (2 H, m), 2.4 (4 H, m), 1.92 (3 H, d, J 3), 1.30 (9 H, s). - ^{19}F-NMR (84.7 MHz) : -51 (d, J 18). - MS (150 °C) : 199 (0.4%, M^+), 57 (100%). - Analysis : calc. for $C_{12}H_{20}FN$ (197.30) C 73.05, H 10.22; found C 72.93, H 10.05%.

***tert*-Butyl-*N*-[2-fluoro-5-methyl-2-(1-methylvinyl)-4-hexenylidene]amine (6b)** : Major component of the 4 : 3 mixture (obtained upon reaction with prenyl bromide; 69%; bp 45 - 50 °C/0.2 mmHg) with *Z*-**7b**; separated by preparative gas chromatography (6 m, 5% SE-30, 130 °C). - ^{1}H-NMR (CCl_4, 60 MHz) : δ 7.53 (1 H, d, J 11), 5.1 (3 H, m), 2.68 (2 H, dd, J 25, 7), 1.7 (6 H, m), 1.18 (9 H, s). - ^{19}F-NMR (84.7 MHz) : -81 (tm, J 25). - Analysis : calc. for $C_{14}H_{24}FN$ (225.35) C 74.62, H 10.73; found C 74.80, H 10.79%.

***(Z)-tert*-Butyl-*N*-(2-fluoro-3,7-dimethyl-2,6-octadienylidene)amine (*Z*-7b)** : Minor component of the 4 : 3 mixture (obtained upon reaction with prenyl bromide; 69%; bp 45 - 50 °C/0.2 mmHg) with **7a**; was directly characterized as its hydrolysis product *Z*-**7b** (see Section 4).

***tert*-Butyl-*N*-[2-fluoro-5,9-dimethyl-2-(1-methylvinyl)-4,8-decadienylidene]amine (6a)** and ***(Z)-tert*-Butyl-*N*-(2-*tert*-Butyl-*N*-(2-fluoro-3,7,11-trimethyl-2,6,10-dodecadienylidene)amine (*Z*-7c)** : Since the 4 : 3 mixture underwent *(Z/E)* equilibration upon attempted distillation or chromatography, it was immediately hydrolyzed under weakly acidic conditions.

4. 2-Fluoro-2-alkenals by Azomethine Hydrolysis

Working procedure : The crude azomethines (20 mmol) were dissolved in diethyl ether (40 mL) and added to a solution of sodium acetate (8.2 g, 0.10 mol) in 50% aqueous acetic acid (40 mL). After 90 min of vigorous stirring, the organic layer was decanted and the aqueous phase extracted with diethyl ether (2 × 50 mL). The combined organic layers were washed with a saturated aqueous solution of sodium hydrogencarbonate (2 × 50 mL) and brine (50 mL). After drying and evaporation of the solvent, volatile residues were distilled (**8a** + *Z*-**9a** : 81%; bp 35 - 40 °C/2 mmHg; **8b** + *Z*-**9b** : 80%; bp 45 - 60 °C/0.5 mmHg) and the components were separated by preparative gas chromatography (**8a** + *Z*-**9b** : 2 m, 5% OV-17, 120 °C; **8b** + *Z*-**9b** : 3 m, 15% UCC-W, 140 °C). The C_{15} aldehyde *Z*-**9c**, however, isomerized at temperatures above 70 °C. Therefore, the regioisomeric aldehydes **8c** and *Z*-**9c** (92%) was separated by column chromatography employing silica gel as the support and a 2 : 98 mixture of ethyl acetate/hexane as the element.

2-Fluoro-2-(1-methylvinyl)-4-pentenal (8a) : IR : 1750 (s). - ^{1}H-NMR (80 MHz) : δ 9.40 (1 H, d, *J* 5), 5.7 (1 H, m), 5.1 (4 H, m), 2.65 (2 H, dd, *J* 24, 7), 1.72 (3 H, s, broad). - ^{19}F-NMR (84.7 MHz) : -92 (td, *J* 24, 6). - MS (180 °C) : 142 (1%, M^+), 123 (13%), 114 (100%). - Analysis : calc. for $C_8H_{11}FO$ (142.17) C 67.59, H 7.80; found C 67.26, H 7.95%.

(Z)-**2-Fluoro-3-methyl-2,6-heptadienal (*Z*-9a)** : IR : 1690 (s). - ^{1}H-NMR (80 MHz) : δ 9.72 (1 H, d, *J* 16), 5.7 (1 H, d, *J* 16), 5.97 (1 H, m), 5.00 (1 H, d, *J* 16), 5.97 (1 H, dm, *J* 10), 2.40 (4 H, m), 2.10 (3 H, d, *J* 3). - ^{1}H-NMR (360 MHz) : δ 9.72 (1 H, *J* 16), 5.83 (1 H, ddt, *J* 16, 10, 7), 5.08 (1 H, dq, *J* 16, 1.5), 5.03 (1 H, dq, *J* 10, 1.5), 2.40 (2 H, td, *J* 7, 2), 2.3 (2 H, m), 2.10 (3 H, d, *J* 3). - ^{19}F-NMR (84.7 MHz) : -57 (d, *J* 15). - MS (180 °C) : 142 (2%, M^+), 114 (100%). - Analysis : calc. for $C_8H_{11}FO$ (142.17) C 67.59, H 7.80; found C 67.78, H 7.85%.

2-Fluoro-5-methyl-2-(1-methylvinyl)-4-hexenal (8b) : IR : 1750 (s). - ^{1}H-NMR ($CDCl_3$, 360 MHz) : δ 9.48 (1 H, d, *J* 5.5), 5.22 (1 H, s), 5.14 (1 H, dt, *J* 4.6, 1.4), 5.09 (1 H, thept, *J* 7.2, 1.4), 2.62 (2 H, dd, *J* 23, 7), 1.72 (6 H, s), 1.65 (3 H, s). - ^{19}F-NMR (84.7 MHz) : -84 (td, *J* 23, 7). - MS (150 °C) : 170 (3% M^+), 141 (25%), 69 (100%). - Analysis : calc. for $C_{10}H_{15}FO$ (170.23) C 70.56, H 8.88; found C 70.63, H 8.99%.

(Z)-**2-Fluoro-3,7-dimethyl-2,6-octadienal (*Z*-9b)** : IR : 1690 (s). - ^{1}H-NMR (80 MHz) : δ 9.72 (1 H, d, *J* 18), 5.1 (1 H, m), 2.35 (2 H, td, *J* 7, 2.5), 2.19 (2 H, q, *J* 7), 2.11 (3 H, d, *J* 3), 1.75 (3 H, s), 1.66 (3 H, s). - ^{19}F-NMR (84.7 MHz) : -52 (d, *J* 18). - MS (150 °C) : 170 (4%, M^+), 141 (10%), 69 (100%). - Analysis : calc. for $C_{10}H_{15}FO$ (170.23) C 70.56, H 8.88; found C 70.54, H 8.88%.

2-Fluoro-5,9-dimethyl-2-(1-methylvinyl)-4,8-decadienal (8c) : IR : 1750 (s). - ^{1}H-NMR (60 MHz) : δ 9.59 (1 H, d, *J* 6), 5.2 (4 H, m), 2.64 (2 H, dd, *J* 25, 7),, 2.1 (4 H, m), 1.7 (6 H, m), 1.6 (6 H, m). - ^{19}F-NMR (84.7 MHz) : -92 (t, *J* 24). - MS (150 °C) : 238 (3%, M^+), 137 (10%), 81 (20%), 69 (100%).

(Z)-**2-Fluoro-3,7,11-trimethyl-2,6,10-dodecatrienal (*Z*-9c)** : IR : 1700 (s). - ^{1}H-NMR (60 MHz) : δ 9.80 (1 H, d, *J* 16), 5.1 (2 H, m), 2.3 (2 H, m), 2.0 (6 H, m), 1.70 (6 H, s, broad), 1.64 (6 H, s). - ^{19}F-NMR (84.7 MHz) : -56 (d, *J* 16). - MS (150 °C) : 238 (3%, M^+), 111 (28%), 69 (100%). - Analysis : calc. for $C_{15}H_{23}FO$ (238.34) C 75.59, H 9.73; found C 75.13, H 10.15%.

5. 2-Fluoro-2-alken-1-ols

Working procedure [17, 18] : Alumina (Merck 507C, activity grade I, 50 g) were heated 24 h to 400 °C under reduced pressure (0.2 mmHg). Diethyl ether (50 mL), isopropyl alcohol (6.0 mL, 4.7 g, 78 mmol) and the 2-fluoro-2-alkenal (10 mmol) were consecutively added. After 3 h of vigorous stirring at 25 °C, methanol (150 mL) was added and the mixture filtered with suction. The solution was evaporated and the residue distilled in a Kugelrohrofen (bulb-to-bulb).

2-Fluoro-5-methyl-2-(1-methylvinyl)-4-hexen-1-ol ("fluorolavandulol", 10b) : 95%; bp 93 - 96 °C/1 mmHg. - ^{1}H-NMR (360 MHz) : δ 5.13 (1 H, tm, *J* 7), 5.05 (2 H, s, broad), 3.71 (2 H, dd, *J* 21.0, 6.5), 2.5 (2 H, m), 1.82 (1 H, t, *J* 6.5), 1.78 (3 H, d, *J* 1 Hz), 1.73 (3 H, d, *J* 1 Hz), 1.64 (3 H, 1 s). - ^{19}F-NMR (84.7 MHz) : -102 (pent, *J* 21.0). - Analysis : calc. for $C_{10}H_{17}FO$ (172.24) C 69.73, H 9.95; found C 69.31, H 10.20%.

(Z)-**2-Fluoro-3,7-dimethyl-2,6-octadien-1-ol ("fluorogeraniol", *Z*-9b)** : 83%; bp 112 - 114 °C/0.2 mmHg. - ^{1}H-NMR (80 MHz) : δ 5.1 (1 H, m), 4.20 (2 H, d, *J* 23), 3.12 (1 H, s), 2.1 (4 H, m), 1.77 (s, broad), 1.70 (3 H, s), 1.67 (3 H, d, *J* 3), 1.60 (3 H, s). - ^{19}F-NMR (84.7 MHz) : -44 (t, *J* 22). - MS (150 °C) : 172 (1%, M^+), 101 (30%), 69 (100%). - Analysis : calc. for $C_{10}H_{17}FO$ (172.24), C 69.73), H 9.95; found C 69.90, H 10.03%.

(*Z/E*)-2-Fluoro-3,7,11-trimethyl-2(*Z*),6(*E*),10-dodecatrien-1-ol ("fluorofarnesol", *Z*-11b : 87%; (by column chromatography). - ^{1}H-NMR (80 MHz) : 5.1 (2 H, m), 4.22 (2 H, d, *J* 23), 2.1 (8 H, m), 1.75 (1 H, s), 1.68 (6 H, s), 1.60 (6 H, s). - ^{19}F-NMR (84.7 MHz) : -44 (t, *J* 22). - MS (170 °C) : 240 (5%, M^+), 197 (25%), 61 (100%). - Analysis : calc. for $C_{15}H_{25}FO$ C 74.96, H 10.48; found C 74.99, H 10.12%.

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